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FIGURES

Figure 1. Flow diagram

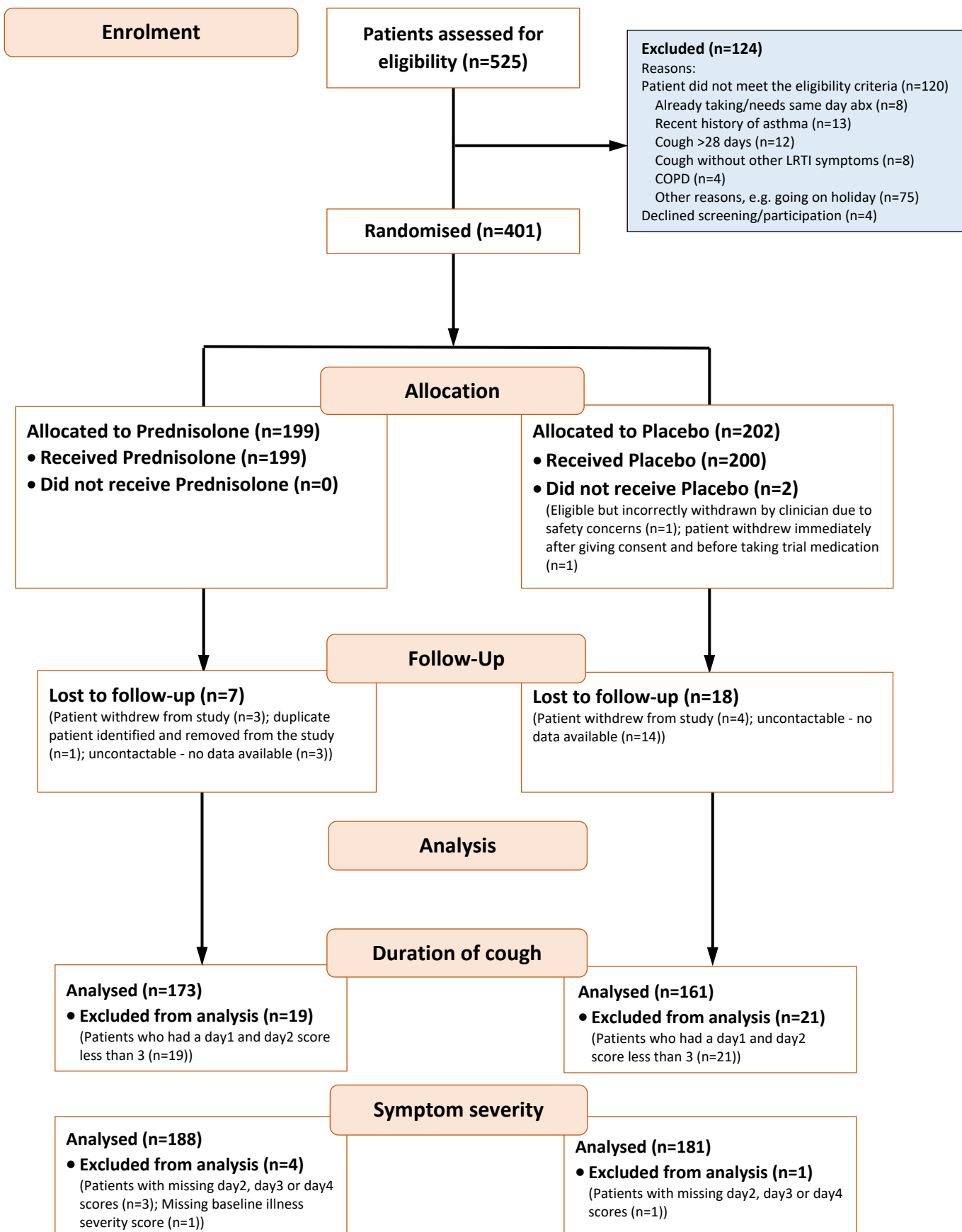
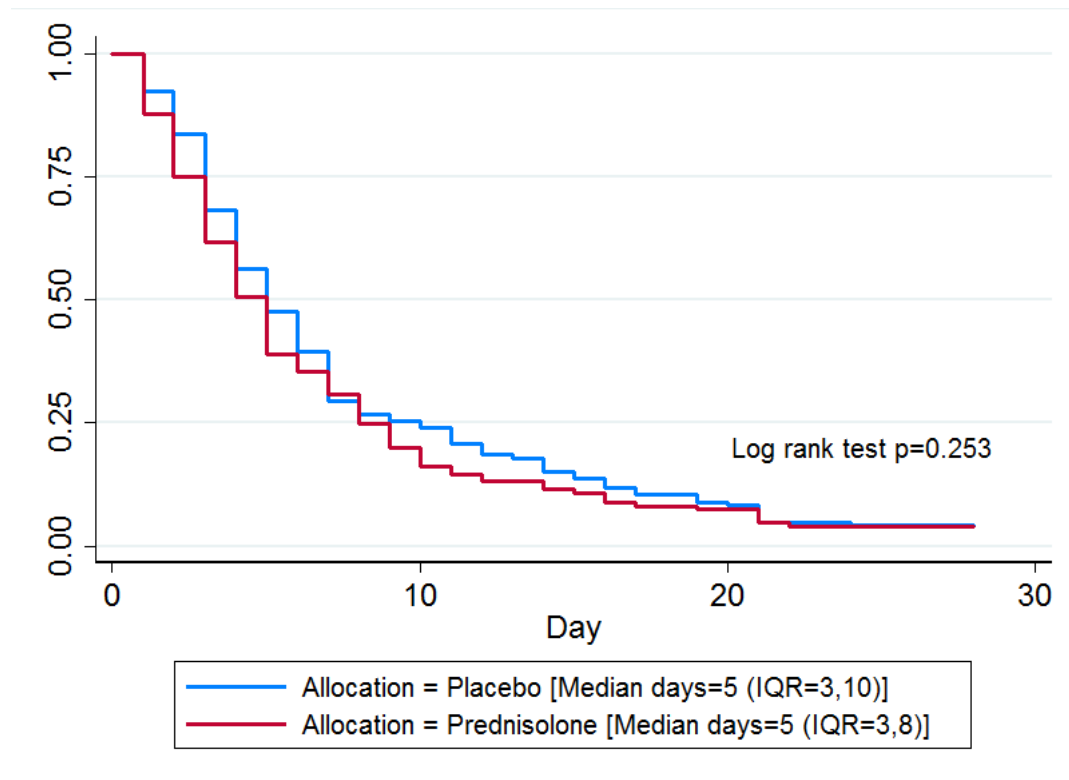


Figure 2. Kaplan Meier curve for time to recovery from moderately bad or worse cough



Number at risk (those left to recover)																												
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Placebo	161	149	135	109	90	76	63	44	40	38	35	30	27	26	22	20	17	15	15	13	12	7	7	7	6	6	6	5
Prednisolone	173	152	129	106	87	66	60	51	41	33	27	24	22	22	17	16	13	12	12	11	11	7	6	6	6	5	5	5

1 **Effect of oral prednisolone on symptom duration in non-asthmatic adults with acute lower respiratory**
2 **tract infection: a randomized clinical trial**

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23 *Keywords*

24 Respiratory tract infections, prednisolone, randomized controlled trials, primary health care

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3563

KEY POINTS

Question: Does a moderate dose of oral corticosteroid reduce the duration or severity of acute lower respiratory tract infection in non-asthmatic adults presenting to primary care?

Findings: In this randomized trial of 401 adults with symptoms of acute lower respiratory tract infection, treatment with oral prednisolone 40 mg daily for 5 days compared with placebo did not significantly reduce the median duration of moderately bad or worse cough (5 days in each group) or the mean severity of symptoms between days 2 and 4 (1.99 vs 2.16 points out of 6)..

26 **Meaning:** These findings do not support the use of oral steroids for the treatment of acute lower
27 respiratory tract infection in the absence of asthma.

28 **ABSTRACT**

29 **Importance:** Acute lower respiratory tract infection is common and often treated inappropriately in
30 primary care with antibiotics. Corticosteroids are increasingly used but without sufficient evidence.

31 **Objective:** To assess the effects of oral corticosteroids for acute lower respiratory tract infection in non-
32 asthmatic adults.

33 **Design, setting and participants:** Multicenter, placebo controlled, randomized trial (July 2013 to final
34 follow-up October 2014) in 54 family practices in England. 401 adults with acute cough and at least one
35 lower respiratory tract symptom, not requiring immediate antibiotic treatment and no history of chronic
36 pulmonary disease or use of asthma medication in past 5 years. Two immediately withdrew, one duplicate
37 patient was identified.

38 **Intervention:** Two 20mg prednisone tablets (n=198) or matched placebo (n=200) once daily for 5 days.

39 **Main outcomes and measures:** Primary - duration of moderately bad or worse cough (0 to 28 days;
40 minimal clinically important difference 3.79 days) and mean symptoms' severity on days 2 to 4 (scored
41 from 0 (not affected) to 6 (as bad as it could be); minimal clinically important difference 1.66 units).
42 Secondary - duration and severity of acute lower respiratory tract infection symptoms; duration of
43 abnormal peak flow; antibiotic consumption; adverse events.

44 **Results:** Among 398 patients with baseline data (mean age 47 (SD 16.0); 63% female; 17% smokers; 77%
45 phlegm; 70% shortness of breath; 47% wheezing; 46% chest pain; 42% abnormal peak flow): 334 (84%)
46 provided cough duration and 369 (93%) symptoms' severity. Median cough duration was 5 days (IQR, 3-8)
47 in the prednisolone group and 5 days (IQR, 3-10) in the placebo group, adjusted HR 1.11 (95% CI 0.89 to
48 1.39, P=0.36, alpha 0.05). Mean symptoms' severities were 1.99 and 2.16, adjusted difference -0.20 (95% CI
49 -0.40 to 0.00, P=0.05, alpha 0.001). No significant treatment effects were observed for duration or severity
50 of acute lower respiratory tract infection symptoms, duration of abnormal peak flow, antibiotic
51 consumption or non-serious adverse events. There were no serious adverse events.

52 **Conclusions and relevance:** Oral corticosteroids should not be used for acute lower respiratory tract
53 infection symptoms in adults without asthma as they do not reduce symptom duration or severity.

54 **Trial registration:** ISRCTN57309858.

55 *Words:* 350

56 INTRODUCTION

57 Acute lower respiratory tract infection (ALRTI), defined as an acute cough with at least one of sputum,
58 chest pain, shortness of breath and/or wheeze,¹ is one of the most common conditions managed in primary
59 care internationally. In 2009 to 2011, an estimated 65% to 75%^{2,3} of patients were prescribed antibiotics,
60 despite good evidence they do not reduce symptom duration or severity,⁴ and guidelines to the contrary.¹
61 Annual antibiotic prescribing costs are estimated at US\$726 million in the US,⁵ and US\$300 million for
62 consultations and antibiotics in the UK.⁶

63

64 Antimicrobial resistance (AMR) is one of the greatest challenges to modern public health.⁷ Primary care is
65 responsible for 80% of health service antibiotic prescribing,^{2,8} with a high proportion regarded as
66 unnecessary² and contributing to AMR.⁹ Both US¹⁰ and UK¹¹ national AMR action plans recommend finding
67 alternatives to antibiotics, but none is currently proven for ALRTI in adults.

68

69 Symptoms of ALRTI are similar to those of exacerbated asthma.¹² Bronchial epithelial changes are similar in
70 people with and without asthma during a RTI, with both groups showing reductions in forced expiratory
71 volume and airways inflammation,¹² and prolonged ALRTI symptoms are thought to be due to bronchial
72 hyper-responsiveness.¹³ Oral and inhaled corticosteroids are highly effective for acute asthma, but US,
73 British and European guidelines do not provide guidance on whether corticosteroids should be used for
74 ALRTI. Despite this, US and European clinicians are increasingly using oral and inhaled steroids, with one US
75 study¹⁴ reporting oral prednisolone use in 15% of non-asthmatic adults with ALRTI.

76

77 A previous systematic review¹⁵ found insufficient evidence regarding the role of inhaled corticosteroids and
78 found no oral corticosteroid studies for ALRTI. The aim of this study was to investigate the effects of a
79 moderate dose of oral corticosteroids in non-asthmatic adults presenting to primary care with ALRTI.

80 **METHODS**

81 **Ethical approval, consent, study design, participant recruitment and baseline assessment**

82 Ethical approval was granted by the Central Bristol Research Ethics Committee (12/SW/0180) and all
83 patients gave informed, written consent. The Oral Steroids for Acute Cough (OSAC) trial was a multicenter,
84 placebo-controlled, individually randomized study, conducted between July 2013 and October 2014. Family
85 physicians and nurses ('recruiting clinicians') were trained in study procedures by four centers at the
86 Universities of Bristol, Southampton, Nottingham and Oxford. They were asked to assess eligibility in
87 consecutive patients: aged ≥ 18 years; consulting for an acute (≤ 28 days) cough as the main symptom with
88 at least one lower respiratory tract symptom (phlegm, chest pain, wheezing or shortness of breath) in the
89 previous 24 hours. Patients were excluded if they: were clinically suspected to have, or their medical
90 records showed evidence of, chronic pulmonary disease; had received any asthma medication in the past 5
91 years; met NICE criteria for severe infection/complications;¹ required same-day hospital admission; or
92 required same day antibiotics (see Online Supplement for full list). Participants were recruited on the day
93 of, or the day following, presentation. Following consent, demographic and clinical data were collected,
94 including self-reported ethnicity using UK approved¹⁶ categories, to assess sample representativeness.

96 **Randomization and concealment**

97 The treatment allocation schedule was computer-generated by a statistician independent of the trial team.
98 Randomization (1:1 ratio prednisolone:placebo) used a variable block size (4, 6, 8 and 10) and was stratified
99 by center. Allocated medication was added to numbered participant packs by pharmacists, independent of
100 the team. All packs were identical and centers distributed four packs to family practices at a time. Following
101 eligibility confirmation, participants were given the next pack.

103 **Intervention and masking**

104 Participant packs contained either 10 prednisolone 20 mg oral tablets (procured GALEN Pharma GmbH,
105 Germany) or matched (dimension, appearance and taste) placebo tablets (Piramal Healthcare Ltd, UK).
106 Participants were asked to take two tablets once daily for five days, starting on the day of consultation, if
107 possible before starting any antibiotics (if receiving a 'delayed' prescription). The dose and duration of
108 prednisolone was selected to reflect the dose and duration known to be effective for acute asthma.¹⁷
109 Participants, recruiting clinicians and the trial team were masked to treatment allocation until data analyses
110 were complete.

112 **Follow up**

113 Participants were invited to report (using web or paper versions) the presence and severity of symptoms
114 using a validated¹⁸ diary shown to be sensitive to change.¹⁹ 4 Symptoms were measured using a scale from
115 zero (no problem) to three (moderately bad) and up to six (as bad as it could be). All symptoms were

116 measured daily, with twice daily peak expiratory flow, for 28 days or until symptom resolution. Cough was
117 measured for a further 28 days in case of late treatment effects. A research nurse telephoned participants
118 weekly to support symptom diary completion. Participants were given £5 (US\$6.6) shopping vouchers at 14
119 and 28 days. Medical notes were reviewed at 3 months for new diagnoses of asthma, COPD, whooping
120 cough and lung cancer.

121

122 **Primary outcomes**

123 Two primary outcomes were used. The first was duration of moderately bad or worse cough, defined as the
124 number of days from randomization to the last day scored ≥ 3 , prior to at least two consecutive days scored
125 < 3 , up to a maximum of 28 days. This was regarded as the more important of the two primary outcomes
126 since cough was the main presenting symptom of the illness, and it included measures of both duration and
127 severity. The second was the mean of the six main symptom (cough, phlegm, shortness of breath, sleep
128 disturbance, feeling generally unwell, and activity disturbance) severity scores (each scored 0-6) on days 2
129 to 4; a mean score was calculated across the symptoms for each day and then an overall mean calculated,
130 giving a maximum value of six.

131

132 **Secondary outcomes**

133 Secondary outcomes specified *a priori* were: total duration and severity of each symptom up to 28 days
134 (cough, phlegm, shortness of breath, wheeze, blocked/runny nose, chest pain, fever, muscle aching,
135 headache, sleep disturbance, feeling generally unwell, activity disturbance); duration of moderately
136 bad/worse and any cough up to 56 days; duration of abnormal peak flow; antibiotic consumption; adverse
137 events; re-consultation with evidence of illness deterioration; patient satisfaction with treatment; and
138 intention to use the same treatment if it were to be available in the future (more detail about the
139 derivation of these outcomes is provided in the Online Supplement). Quality of life, NHS treatment and
140 investigation costs are not reported in this article.

141

142 **Subgroup analyses**

143 Pre-specified potential treatment effect modifiers were: age; prior cough duration; presence of wheeze;
144 antibiotic consumption; β -agonist consumption; smoking status; history of hay fever, asthma or eczema;
145 new diagnoses (at 3 months) of asthma, COPD, whooping cough or lung cancer. Baseline impression of
146 severity of illness was added as a *post-hoc* sub group analysis as the trial team determined it was important
147 to differentiate between those with severe vs. mild symptoms.

148

149 **Sample size calculation**

150 The distributions of both primary outcomes were expected to be positively skewed, hence sample size
151 calculations were based on the log-normal distribution. The mean (standard deviation (SD)) duration of

152 moderately bad or worse cough and symptom severity score (days 2 to 4) were estimated as 5.8 (4.1) days
153 and 2.3 (1.1) units respectively.¹⁹ This corresponds to 1.56 (SD 0.64) log days (or geometric mean of 4.74
154 days) for cough duration and 0.73 (SD 0.45) units on the log scale (or geometric mean of 2.08) for symptom
155 severity. As there were no previous studies of oral steroids to inform the minimum clinically important
156 difference (MCID) in both outcomes, the investigative team considered the balance of potential benefits
157 and adverse effects, and reached a MCID consensus of 20%, corresponding to a geometric mean in the
158 active treatment group of 3.79 days (mean 1.33 log days) in terms of duration of cough and 1.66 units
159 (mean 0.51 log units) for symptom severity. Allowing for 20% attrition, 218 participants needed to be
160 randomized per group to retain 174 at follow-up and achieve 90% power with a two-sided alpha of 0.05 for
161 primary outcome one. A final achieved sample size of 174 participants per group would provide 89% power
162 to detect a 20% reduction in symptom severity, with an adjusted two-sided alpha of 0.001 to reflect its
163 'second primary outcome' status (see Online Supplement).

164 **Statistical methods**

165 *Analysis of primary outcomes*

166 A pre-specified analysis plan was approved by the Trial Steering and Data Monitoring Committees and the
167 study protocol was published before data collection had finished (see Online Supplement). All analyses
168 were performed in Stata 13.1.²⁰

169 The primary comparative analyses considered patients in the groups to which they were randomized,
170 without imputation for missing outcome data. These analyses were adjusted for center (Bristol,
171 Nottingham, Oxford and Southampton), and the relevant baseline measure (prior cough duration (1-28
172 days) for duration of moderately bad or worse cough; patient reported illness severity in last 24 hours for
173 symptom severity (0 completely well – 10 extremely unwell). Time-to-event methods were used to analyze
174 the duration of moderately bad or worse cough. Semi-parametric Cox-proportional hazard models were
175 employed (to enable comparison with previous studies) and the assumption of proportional hazards
176 checked by visual inspection of the log-log survival curves and calculation of the Schoenfeld residuals.²¹
177 Hazard ratios were reported comparing the instantaneous rate of resolution of cough between
178 prednisolone and placebo groups, with 95% confidence intervals (CI) and P values. In order to assist
179 interpretation against the MCID of a 20% reduction in time to resolution, for which hazard ratios are
180 unhelpful, parametric Weibull Accelerated Failure Time (AFT) models were used to present cough duration
181 treatment effects as time ratios. Such models can be formulated as proportional hazards or AFT models;
182 hence hazard ratios were also produced from the Weibull models to ensure comparability with the Cox
183 models.

184 Mean severity score from days 2 to 4 was considered in linear regression models. Models considered mean
185 severity score and log mean severity score and distributional checks of residuals were undertaken to

186 determine the most appropriate model. Differences between the prednisolone and placebo groups are
187 reported with 95% confidence intervals and P-values.

188 For both primary outcomes, secondary analyses additionally adjusted for factors demonstrating imbalance
189 at baseline (a difference >5% for binary and >0.5SDs for continuous outcomes) and for smoking, since this is
190 known to be prognostically important.¹⁵

191 *Analysis of secondary outcomes, subgroup analyses and sensitivity analyses*

192 Analyses of secondary outcomes used regression models as appropriate. Consideration of potential effect
193 modifiers employed formal tests of interaction. Sensitivity analyses considered multiple imputation of
194 missing data (using a two-fold fully conditional specification algorithm),^{22 23} treatment adherence, day of
195 recruitment, and inclusion of those with no moderately bad or worse cough at baseline (*post-hoc*). See
196 Online Supplement for details.

197

198

199 RESULTS

200 Enrolment and study population

201 58 family physicians and 50 practice nurses based in 54 family practices assessed 525 patients for
202 suitability, of whom 401 were eligible, consented and randomized: 199 to prednisolone and 202 to placebo
203 (Figure 1), equating to a mean patient recruitment rate of 0.5 patients per month per practice. Two placebo
204 group patients requested complete withdrawal immediately post randomization, and a further duplicate
205 patient was subsequently identified in the prednisolone group (the participant remained in the group to
206 which they were first allocated) leaving a sample of 398. The trial was stopped when the required number
207 of participants was achieved. At baseline, participants had a mean age of 47.4 (SD 16.0) years; 37% were
208 male; 3.5% had diabetes, 17% were currently smoking; 5% had received asthma medication more than 5
209 years previously; 77% reported phlegm; 46% chest pain; 47% wheezing; 70% shortness of breath; and 42%
210 had abnormal (defined as <80% expected) peak flow. Baseline characteristics were similar between the
211 groups with respect to deprivation, smoking status, weight, height and clinical characteristics of the ALRTI,
212 though compared to placebo, the prednisolone group were slightly more likely to be male, older (and
213 hence retired), and to have received an influenza vaccine in the last 12 months (Table 1).

215 Primary outcome data completeness

216 Symptom diaries were returned by 374 (94%) participants (192 prednisolone and 182 placebo). For
217 duration of moderately bad or worse cough, data were available in 334 (84%) participants with 40 reporting
218 an initial cough severity <3 (that is, not moderately bad or worse) and 24 lost to follow up. For symptom
219 severity, follow-up data were available in 370 (93%). However, one participant in the prednisolone group
220 had no baseline measure of illness severity and could not be used in the adjusted analysis. Patients who
221 withdrew or were lost to follow up were younger (median 30 years vs. 49 years), less likely to be white
222 (85% vs 97%), more likely to be employed (86% vs. 69%) and higher English Index of Multiple Deprivation
223 score (18 vs. 11).

225 Primary analyses

226 *Moderately bad or worse cough duration*

227 The median duration of moderately bad or worse cough was 5 days (IQR, 3-8) in the prednisolone group
228 and 5 days (IQR, 3-10) in the placebo group (Table 2). Kaplan Meier survival curves were similar for both
229 groups (Figure 2). Visual inspection of the log-log survival curves and calculation of the Schoenfeld residuals
230 ($P=0.52$) provided no evidence against proportional hazards. Comparing prednisolone with placebo, the Cox
231 model adjusting for center and baseline cough duration resulted in a hazard ratio of 1.11 (95% CI 0.89, 1.39;
232 $P=0.36$ with alpha of 0.05). The hazard ratio represents the instantaneous risk of resolution from
233 moderately bad or worse cough in the prednisolone group compared to placebo; a hazard ratio greater
234 than 1 demonstrates a beneficial effect of prednisolone. The Weibull AFT model time ratio was 0.91 (95% CI

0.76, 1.10) indicating that the time to resolution was reduced by 9% (0.45 days) with prednisolone compared to placebo (P=0.34); the lower limit of the 95% CI did not exclude the 20% *a priori* minimum clinically important difference. Further (secondary analysis) adjustment for factors demonstrating possible imbalance at baseline (age, gender, influenza vaccine in last 12 months) and smoking, had no effect on the models (Table 2).

240

Day 2 to 4 symptom severity

Mean symptom severity scores (and residuals) were normally distributed. The mean (SD) symptom severity scores were 1.99 (0.99) and 2.16 (1.09) for the prednisolone and placebo groups respectively. Adjusting for center and baseline illness severity, the mean symptom severity difference was 0.20 (95% CI -0.40, 0.00, P=0.05) between prednisolone and placebo (Table 2, *a priori* alpha 0.001). With a mean symptom severity score of 2.16 in the placebo group, a difference of 0.20 equates to a relative reduction of 9.3%. The lower limit of the 95% CI of this reduction was 18.5%, and excluded the 20% *a priori* minimum clinically important difference. Additional adjustment for factors demonstrating imbalance at baseline and smoking, marginally attenuated the difference in means and reduced the strength of evidence against the null hypothesis (Table 2).

251

Sensitivity analyses (see Online Supplement)

None of the sensitivity analyses had any effect on the primary comparisons: including those with no moderately bad or worse cough at baseline; multiple imputation of missing data; per protocol analysis; adjusting for day of recruitment (Web Table 1).

256

Secondary outcomes

There were no significant effects on any symptom duration or peak flow up to 28 days, or cough duration to 56 days (Table 3). Neither were any significant effects observed for: antibiotic use; patient satisfaction or intention to use the same treatment if it were to be available in the future; non-serious adverse events (Table 3), expected, unexpected or cough-related adverse events, or reconsultations (Web Table 2). The nature of the adverse events was similar between the groups (Web Table 3), no new urinary or visual symptoms were reported, and none of the patients reporting fatigue, thirst and dry throat (Web Table 3) had diabetes. There were no serious adverse events. Four participants (3 prednisolone and 1 placebo) attended accident and emergency but were not hospitalized.

266

Absolute measures of between-group differences

To aid interpretation, Table 4 presents absolute measures of effect for the primary outcome of duration of moderately bad or worse cough and the time-to-event secondary outcomes reported in Table 3. There is no single absolute measure of treatment effect for time-to-event data as it will vary over the duration of

271 follow-up; it can, however, be calculated at a specific time point. Of particular clinical interest is day 7,
272 because this is a time in the illness trajectory when clinicians and patients want to know about expected
273 benefits, and when steroids should have affected symptoms if effective. Survival curves were produced
274 from the Cox regressions presented in Tables 2 and 3 at given values of center (Bristol) and duration of
275 prior cough (median value). Predicted survival probabilities at day 7 in the prednisolone and placebo groups
276 were obtained and an absolute risk difference estimated as the survival probability in the prednisolone
277 group minus that in the placebo group. 95% confidence intervals were obtained using the method
278 proposed by Altman and Andersen.²⁴ As an example of interpretation, for duration of moderately bad or
279 worse cough the absolute difference in percentage unresolved at day 7 is -3.61 (95% CI -10.64, 4.23); this
280 can be interpreted as 3.61% fewer prednisolone patients who still have an unresolved moderately bad or
281 worse cough at the end of day 7. Absolute risk differences were also obtained (with 95% confidence
282 intervals) for the binary secondary outcomes of antibiotic use (up to 7 and 28 days), patient satisfaction and
283 intention to use the same treatment if it were to be available.

284

285 **Subgroup analyses**

286 All 95% confidence intervals for the interaction effects included values consistent with no significant
287 subgroup effect (Web Table 4).

288 DISCUSSION

289 In this randomized trial of 401 adults, five days of moderate dose oral prednisolone did not reduce the
290 duration of moderately bad or worse cough, or the severity of symptoms between days 2 and 4, in non-
291 asthmatic adults who presented to primary care with ALRTI. Neither were any effects observed for the
292 duration and severity of any ALRTI symptom, the duration of abnormal peak flow, antibiotic consumption
293 or adverse events, including worsening of glycemic control in patients with diabetes.

294

295 The study has several strengths. It was an adequately powered, multicenter, fully masked, randomised trial,
296 with low rates of missing baseline and follow up data. The design was pragmatic, using eligibility criteria
297 easily reproduced in routine clinical practice and clinically relevant, validated¹⁸ outcomes. The final sample
298 included participants with high rates self-reported sputum production and wheeze, and was generalizable
299 to non-asthmatic adults presenting to primary care with ALRTI in whom an immediate antibiotic is not
300 necessary. With 398 participants, this trial more than doubles the number of patients recruited to primary
301 care trials of corticosteroids for ALRTI,¹⁵ and to our knowledge, is the first to investigate the effects of oral
302 rather than inhaled steroids. The trial also contributes to a growing body of evidence suggesting systemic
303 and topical corticosteroids have a limited role in the treatment of common infections and their post-
304 infectious complications in primary care.^{25,26} This contrasts with an increasing number of studies suggesting
305 corticosteroids are effective for secondary care patients with community acquired pneumonia²⁷ croup,²⁸
306 acute sinusitis²⁹ and severe sore throat.³⁰

307

308 This study also has several limitations. First, the low patient recruitment rate suggests patients may have
309 been selectively invited to participate, affecting the generalizability of the final sample. However, the rate
310 was faster than a similar previous trial,¹⁹ not all practices were active throughout the recruitment period,
311 and the characteristics of the final sample appears representative of primary care adult patients with ALRTI.
312 Second, there were a higher than expected number of participants with zero duration of moderately bad or
313 worse cough, though a sensitivity analysis including these participants did not influence the results. Third,
314 other baseline biomarkers (e.g. inflammatory, microbiological, spirometric or radiographic) were not
315 measured and it is possible that patients with more severe, inflammatory, eosinophilic^{31,32} or
316 microbiological (e.g. rhinovirus)³³ etiology entered the trial or could have differentially benefited. However,
317 the study used readily recognized, pragmatic entry criteria facilitating replication in routine clinical practice.
318 Fourth, study eligibility criteria might have included some patients with chronic or postinfectious cough,
319 rather than ALRTI. However, 100% of participants had evidence of active lower respiratory tract
320 involvement (sputum, shortness of breath, wheeze or chest pain) and over 75% had a pre-consultation
321 cough duration <21 days. Fifth, the study used a patient-reported outcome rather than an objective
322 primary outcome measure (such as digitally measured cough severity). This was chosen because it was
323 considered the strongest option in the presence of a fully masked intervention; it closely reflected patient

324 priorities; and it allowed comparison with other trials.^{4,19} Sixth, the lack of effects and a similar between-
325 group pattern of adverse events could reflect poor adherence. However, this is unlikely as standard
326 methods³⁴ were used to establish similar and high levels of adherence to both prednisolone and placebo,
327 and adverse events were similar to another trial in which a similar dose of prednisolone was proven
328 effective.³⁴

329

330 The trial suggests oral corticosteroids should not be used in non-asthmatic/non-COPD adults in primary
331 care who do not require treatment with an immediate antibiotic. Further research is needed to establish
332 effectiveness in primary care patients with more severe infections, such as those with raised C-reactive
333 protein, or requiring immediate antibiotic treatment, and larger studies or meta-analysis are needed to
334 address effects in subgroups, such as those with longer pre-consultation illness and non-smokers.¹⁵

335

336 **Conclusions**

337 Among adults without asthma who developed ALRTI, the use of oral prednisolone for five days did not
338 reduce symptom duration or severity. These findings do not support oral steroids for treatment of ALRTI in
339 the absence of asthma.

340

341 **AUTHOR CONTRIBUTIONS**

342 Alastair Hay (ADH) was responsible for overall study design, management and data interpretation. ADH led
343 the writing of, and approved, the final manuscript. Paul Little (PL), Michael Moore (MVM), Anthony
344 Harnden (AH), Matthew Thompson (MT), Kay Wang (KW), Denise Kendrick (DK), Elizabeth Orton (EO),
345 Sandra Hollinghurst (SPH) and Fran Carroll (FC) made substantial contributions to overall study design and
346 to writing, and reviewed the final manuscript. Margaret May (MM) contributed to the design of statistical
347 analyses and reviewed the final manuscript. Sara Brookes (STB) was lead study statistician and had full
348 access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of
349 the data analysis. She led the data analyses, contributed to the writing and reviewed the final manuscript.
350 Grace Young (GY) conducted the data analysis, writing and reviewed the final manuscript. Harriet Downing
351 (HD) was the study manager, contributed to and reviewed the final manuscript. David Timmins (DT), Kate
352 Martinson (KM) and Natasher Lafond (NL) were study co-ordinators, and contributed to and reviewed the
353 final manuscript. ADH is guarantor for the study and affirms that the manuscript is an honest, accurate, and
354 transparent account of the study being reported; that no important aspects of the study have been
355 omitted; and that any discrepancies from the study as planned have been explained.

356

357 **CONFLICT OF INTEREST DISCLOSURES**

358 All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.
359 Dr Thompson reported that he has received funding from Alere Inc to conduct research on C-reactive
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362

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366

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368 The sponsor was the University of Bristol. Neither the funder nor the sponsor had no involvement in the
369 design and conduct of the study; collection, management, analysis, and interpretation of the data;
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371

372 **DISCLAIMER**

373 The views expressed herein are those of the authors and not necessarily those of the NIHR, the National
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375

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386

389 **Table 1. Baseline characteristics of randomized patients, by treatment group**

	Prednisolone (N=198)	Placebo (N=200)
Center, n (%)		
Bristol	118 (60%)	113 (57%)
Oxford	39 (20%)	45 (23%)
Southampton	24 (12%)	21 (11%)
Nottingham	17 (9%)	21 (11%)
<i>Demographics and past medical history</i>		
Gender, n (%) male	82 (41%)	66 (33%)
Age in years, mean (SD)	50.0 (16.1)	44.8 (15.5)
Weight kg, median (IQR) ^a	77.0 (64.5,91.0)	76.0 (66.5,90.5)
Height cm, median (IQR) ^b	168.0 (161.0,175.0)	168.0 (163.0,176.0)
Ethnicity, n (%) white ^c	188 (95%)	193 (97%)
Occupation, n (%)		
Employed	137 (69%)	143 (72%)
Unemployed	17 (9%)	21 (11%)
Retired	41 (21%)	30 (15%)
Full-time education	3 (2%)	6 (3%)
Deprivation (IMD) ^d , median (IQR) ^e	11.0 (5.0,23.0)	12.0 (5.0,23.0)
Smoking status, n (%) ^f		
Current	31 (16%)	38 (19%)
Past	63 (32%)	55 (28%)
Never	104 (53%)	106 (53%)
Lives with smoker, n (%) ^g	25 (14%)	32 (16%)
Received asthma medication >5 years previously ^h	10 (5%)	8 (4%)
Personal history of hay fever ⁱ	41 (22%)	46 (24%)
Personal history of eczema ^j	30 (16%)	26 (14%)
Family history asthma or hay fever or eczema, n (%) ^k	73 (40%)	76 (40%)
Influenza vaccine in last 12 months, n (%)	63 (32%)	44 (22%)
Recruited in winter (1 st Oct-31 st March)	112 (57%)	114 (57%)
<i>Clinical characteristics and management</i>		
Prior duration of cough (days), median (IQR)	13.0 (7.0,20.0)	10.0 (6.0,17.5)
Sputum (present within last 24 hours), n (%) ^l	149 (76%)	156 (78%)
Shortness of breath (present within last 24 hours) n (%)	146 (74%)	133 (67%)
Wheeze (present within last 24 hours), n (%) ^l	88 (45%)	98 (49%)
Chest pain (present within last 24 hours) n (%)	88 (44%)	97 (49%)
Patient reported illness severity at assessment (0-10), median (IQR) ^m	6.0 (5.0,7.0)	5.0 (4.0,7.0)
Pulse rate (bpm), mean (SD)	77.8 (12.3)	77.7 (11.8)
Temperature (°C), mean (SD)	36.6 (0.5)	36.6 (0.4)
Oxygen saturation (%), mean (SD) ⁿ	97.5 (1.3)	97.8 (1.1)
Abnormal peak flow (less than 80% of expected peak)	87 (44%)	79 (40%)

flow) ^o		
Respiratory rate (breaths per minute) ^p	15.4 (2.5)	15.0 (2.4)
Abnormal respiratory rate (more than 20 breaths per minute), n (%)	2 (1%)	1 (1%)
Chest retraction or prolonged expiration	0 (0%)	1 (1%)
Wheeze or rhonchi (auscultation), n (%)	11 (6%)	11 (6%)
Crackles or crepitations (auscultation), n (%) ^q	4 (2%)	6 (3%)
Bronchial breathing, n (%)	0 (0%)	2 (1%)
Taken prescribed β agonist in past 24 hours, n (%)	9 (5%)	3 (2%)
Over-the-counter drugs taken for current cough, n (%)	128 (65%)	139 (70%)
Given delayed antibiotic prescription, n (%)	22 (11%)	25 (13%)

390 ^a Weight missing for 2 prednisolone participants

391 ^b Height missing for 1 prednisolone participant

392 ^c Ethnicity missing for 1 placebo participant

393 ^d English Index of Multiple Deprivation scores (2015) [Geoconvert: UK Data Service Census Support], possible range 0-
394 100; higher scores indicate higher levels of deprivation

395 ^e IMD missing for 2 prednisolone and 7 placebo participants

396 ^f Smoking status missing for 1 placebo participant

397 ^g Living with smoker missing for 15 prednisolone and 5 placebo participants

398 ^h Personal history of asthma missing for 10 prednisolone patients and 7 placebo patients

399 ⁱ Personal history of hayfever missing for 10 prednisolone patients and 11 placebo patients

400 ^j Personal history of eczema missing for 14 prednisolone patients and 10 placebo patients

401 ^k Family history of hay fever or eczema or asthma missing for 16 prednisolone and 11 placebo participants

402 ^l Sputum and wheeze presence in last 24 hours, missing for 1 prednisolone participant

403 ^m Patient reported illness severity 0 (completely well) to 10 (extremely unwell), missing for 1 prednisolone participant

404 ⁿ Oxygen saturation missing for 1 prednisolone participant

405 ^o Baseline abnormal peak flow was missing for 1 prednisolone patient

406 ^p Respiratory rate missing for 2 prednisolone and 1 placebo patient as only collected for those with a 'normal' rate

407 ^q Includes unilateral and bilateral

408 **Table 2. Primary analyses**

	Prednisolone		Placebo		Prednisolone vs. placebo			
	N	Median (95% CI)	N	Median (95% CI)	Hazard ratio (95% CI)	P value (alpha=0.05)	Time Ratio ^a (95% CI)	P value (alpha=0.05)
Duration (days) of moderately bad or worse cough (censored at 28 days)	173	5 (4,5)	161	5 (4,6)				
Adjusted for center and baseline ^b					1.11 (0.89, 1.39)	0.36	0.91 (0.76, 1.10)	0.34
Secondary additional adjustment ^{c,d}					1.09 (0.87, 1.37)	0.44	0.92 (0.76, 1.12)	0.40
	N	Mean (95% CI)	N	Mean (95% CI)	Difference in means (95% CI)			P value (alpha=0.001)
Mean symptom severity score (days 2-4) ^e	188	1.99 (1.85, 2.13)	181	2.16 (2.00, 2.32)				
Adjusted for center and baseline ^{b,f}					-0.20 (-0.40, 0.00)			0.054
Secondary additional adjustment ^{c,d,f}					-0.17 (-0.37, 0.04)			0.110

409 ^a Time ratio can be interpreted as the relative increase or decrease in time to resolution of moderately bad or worse cough in the prednisolone group compared to placebo group

410 ^b Baseline measure for duration of cough is prior duration of cough (1-28 days) and for mean symptom severity score is patient reported illness severity (0 – 10).

411 ^c Adjusted for center, baseline (as detailed in footnote b), factors showing baseline imbalance (age, gender, influenza vaccine) and smoking

412 ^d Smoking status missing for 1 placebo participant

413 ^e See *Methods, Primary Outcomes* for derivation of mean symptom severity score (minimum of 0 and maximum of 6 (most severe)).

414 ^f Patient reported illness severity missing for 1 prednisolone participant

415

416 **Table 3. Secondary outcomes**

	Prednisolone (N=192)	Placebo (N=182)	Prednisolone vs. placebo Adjusted for center and baseline^a	
	Mean area under curve ^{b,c} (95% CI)	Mean area under curve ^{b,c} (95% CI)	Difference in mean area under curve (95% CI)	P value
Cough	40.16 (36.67, 43.65)	42.88 (38.88, 46.87)	-2.43 (-7.66, 2.80)	0.36
Phlegm	25.48 (22.19, 28.78)	30.01 (26.40, 33.61)	-4.10 (-8.89, 0.70)	0.09
Shortness of breath	16.10 (13.25, 18.95)	18.39 (15.16, 21.61)	-2.30 (-6.34, 1.75)	0.27
Wheeze	12.32 (9.69, 14.96)	13.24 (10.37, 16.11)	0.18 (-3.27, 3.64)	0.92
Blocked or runny nose	19.83 (16.38, 23.28)	20.06 (17.12, 23.00)	0.67 (-3.70, 5.05)	0.76
Chest pain	6.64 (4.95, 8.33)	9.59 (6.98, 12.19)	-2.92 (-5.83, -0.01)	0.05
Fever	2.98 (2.05, 3.91)	3.45 (2.07, 4.82)	-0.33 (-1.90, 1.24)	0.68
Muscle ache	8.83 (6.71, 10.96)	10.29 (7.53, 13.06)	-1.61 (-4.99, 1.77)	0.35
Headache	10.77 (8.27, 13.28)	11.83 (8.89, 14.77)	-0.62 (-4.34, 3.09)	0.74
Sleep disturbance	20.80 (17.66, 23.94)	22.11 (18.13, 26.10)	-0.75 (-5.60, 4.10)	0.76
Feeling generally unwell	19.83 (17.22, 22.45)	22.68 (19.17, 26.19)	-3.25 (-7.38, 0.89)	0.12
Activity disturbance	14.29 (12.01, 16.57)	19.07 (15.40, 22.74)	-4.78 (-8.86, -0.69)	0.02
	Median (95% CI) ^g	Median (95% CI) ^g	Hazard ratio (95% CI)	P value
Duration (days) of moderately bad or worse cough (censored at 56 days) ^d	5 (4,5)	5 (4,6)	1.11 (0.89, 1.39)	0.36
Duration (days) of any cough (censored at 56 days) ^e	18 (17,23)	20 (17, 25)	1.13 (0.90, 1.42)	0.29
Duration (days) of abnormal peak flow (censored at 28 days) ^f	10 (7, 17)	11 (8,17)	1.10 (0.79, 1.52)	0.58

Table 3 continued

	Prednisolone (N=192)	Placebo (N=182)	Prednisolone vs. placebo Adjusted for center and baseline^a	
	n, (% {95% CI}) ⁱ	n, (% {95% CI}) ⁱ	OR (95% CI)	P value
Consumption of antibiotics				
Up to 7 days	15, (8 {4, 12})	15, (8 {4, 12})	0.98 (0.42, 2.28)	0.96
Up to 28 days	28, (15 {10, 20})	34, (19 {13, 24})	0.78 (0.44, 1.39)	0.39
Patient satisfaction: Participant agrees trial tablets helped them feel better ^h	60, (34 {27, 41})	43, (25 {19, 32})	1.46 (0.92, 2.34)	0.11
Participant agrees they would take trial tablets in future ⁱ	99, (56 {48, 63})	81, (47 {40, 55})	1.36 (0.89, 2.08)	0.16
Any adverse events ^j				
0	151 (77 {71, 83})	162 (82 {76, 87})	1.26 (0.77, 2.07) ^k	0.36
1	36 (18 {13, 25})	24 (12 {8, 17})		
>1	9 (5 {2, 9})	12 (6 {3, 10})		

^a Baseline measure for cough area under curve (AUC), duration of moderately bad or worse cough (56 days), any cough (56 days) and abnormal peak flow is prior duration of cough (days); for all symptoms (AUC) (with the exception of cough) baseline measure is presence or absence of symptom at baseline (previous 24 hours); and for antibiotic consumption, whether participant given delayed antibiotic prescription (Y/N). No baseline measures available for patient satisfaction, taking tablets in future or adverse events.

^b For derivation of symptom area under curve see *Online supplement: Methods, Statistical analyses, Analysis of secondary outcomes*.³⁵

^c Missing data - AUC analysis includes: 185 prednisolone and 179 placebo participants for cough; 184 prednisolone and 179 placebo participants for phlegm, shortness of breath; 183 prednisolone and 179 placebo participants for wheeze, sleep disturbance; 182 prednisolone and 179 placebo participants for blocked or runny nose, chest pain, fever, muscle ache, headache, feeling generally unwell, activity disturbance.

^d 5 patients in each group had unresolved moderately bad or worse cough at day 28. Total duration (up to 56 days) obtained for 3 prednisolone and 5 placebo patients.

^e 61 prednisolone and 63 placebo patients had unresolved cough (score<1) at day 28. Total duration (up to 56 days) obtained for 38 prednisolone and 50 placebo patients.

^f 18 prednisolone and 25 placebo patients had abnormal peak flow at 28 days. Post-hoc sensitivity analysis removed 6 prednisolone patients rated at baseline as poor at measuring peak flow – there was no impact on the model.

^g Missing data - Duration of moderately bad or worse cough (56 days) analysis includes 173 prednisolone and 161 placebo participants (participants without moderately bad or worse cough on day 1 excluded); duration of any cough (56 days) analysis includes 191 prednisolone and 182 placebo participant; duration of abnormal peak flow analysis includes 117 prednisolone and 115 placebo participants (participants with normal peak flow on day 1 excluded).

^h For derivation see *Online supplement: Methods, Statistical analyses, Analysis of secondary outcomes*

ⁱ Missing data - Antibiotic consumption analyses include 191 prednisolone and 182 placebo participants; patient satisfaction analyses include 178 prednisolone and 171 placebo.

^j Excludes the duplicate participant who did experience an expected adverse event during their duplicate entry

^k Ordinal logistic regression, adjusting for center and baseline patient reported illness severity, missing for 1 participant.

435 **Table 4: Estimates of absolute between-group differences for time-to-event and binary outcomes**

Time-to-event outcomes	Prednisolone			Placebo			Absolute difference in % unresolved ^b (95% CI) Adjusted for center and baseline ^c
	N ^a	Unresolved at end of day 7		N ^a	Unresolved at end of day 7		
		n	% (95% CI)		n	% (95% CI)	
Duration (days) of moderately bad or worse cough	173	51	30.64 (23.89, 37.63)	161	44	29.19 (22.33, 36.38)	-3.61(-10.64, 4.23)
Duration (days) of any cough	191	164	88.36 (82.86, 92.18)	182	154	88.91 (83.34, 92.70)	-1.28 (-4.07, 1.00)
Duration (days) of abnormal peak flow	117	62	59.26 (49.56, 67.71)	115	63	60.32 (50.67, 68.67)	-2.89 (-14.10, 6.83)
Binary outcomes	N ^a	n	% (95% CI)	N ^a	n	% (95% CI)	Absolute difference in % (95% CI) Adjusted for center and baseline ^d
Consumption of antibiotics	191			182			
Up to 7 days		15	7.85 (4.00, 11.70)		15	8.24 (4.21, 12.28)	-0.09 (-5.13, 4.94)
Up to 28 days		28	14.66 (9.60, 19.72)		34	18.68 (12.96 24.40)	-3.26 (-10.53, 4.02)
Patient satisfaction: Participant agrees trial tablets helped them feel better	178	60	33.71 (26.70, 40.72)	171	43	25.15 (18.88, 31.71)	7.74 (-1.85, 17.34)
Participant agrees they would take trial tablets in future	178	99	55.62 (48.25,62.99)	171	81	47.37 (39.81, 54.93)	7.48 (-3.02, 17.97)

436 ^a N refers to the number of participants with data available for the outcome of interest and included in the analysis.

437 ^b Absolute difference is calculated as the percentage unresolved at end of day 7 in prednisolone group minus the percentage in placebo group. A negative value for the absolute

438 risk difference indicates that a smaller percentage of prednisolone patients will have unresolved cough or abnormal peak flow at end of day 7 than placebo patients.

439 ^c For time-to event outcomes adjusted analyses consider an ‘average’ value of covariates: Center = Bristol (where 60% of patients were recruited from) and prior duration of cough

440 = 12 days (median value in sample).

441 ^d Baseline measure for consumption of antibiotics is whether participant was given delayed antibiotic prescription at baseline (Y/N). No baseline measures available for patient

442 satisfaction or taking tablets in future.

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